REMARKS

Claims 82 and 93-107 are pending. Claims 93-94 and 97-104 are withdrawn from consideration as being directed to non-elected subject matter. Claims 82, 95-96 and 105-107 were rejected in the Office Action of November 2, 2007.

I. Interview Summary

Applicants thank Examiner Soroush and Supervisory Examiner Richter for the courtesy of a telephone interview with the undersigned and Dr. Ann-Louise Kerner on February 6, 2008. The outstanding obviousness rejection of the pending claims was discussed.

In particular, the Examiner focused on U.S. Patent No. 5,498,607 to Hsia et al. ("Hsia") as the primary reference. Applicants pointed out, as discussed in more detail below, that Hsia is directed to treating atherosclerosis with a topical composition containing a phospholipid while, in stark contrast, Applicants' claims recite a topical pharmaceutical composition for reducing skin pigmentation that includes a compound of formulas II-VIII, which are not phospholipids. Thus, the only commonality between Hsia and Applicants' claims is that both disclose topical formulations.

The Examiners agreed to reconsider the rejections in view of Applicants' arguments as presented below, and in particular to fully consider the unexpected results presented in Applicants' specification.

II. Rejections Under 35 U.S.C. § 103(a)

Claims 82, 95-96 and 105-107 were rejected as allegedly being obvious over U.S. Patent No. 3,389,051 to Kagan ("Kagan") in combination with one or more of U.S. Patent No. 5,498,607 to Hsia et al. ("Hsia"), U.S. Patent No. 5,589,192 to Okabe et al. ("Okabe") and U.S. Patent No. 6,020,323 to Cohen et al. ("Cohen"). Applicants respectfully traverse these rejections.

Applicants' independent claim 82 recites a pharmaceutical composition for reducing skin pigmentation. The pharmaceutical composition is an ointment, cream, lotion or emulsion formulated for percutaneous absorption by topical administration, and includes a skin pigmentation reducing effective amount of a compound and a dermatologically-acceptable carrier. The compound is selected from chemical structures II-VIII, pharmaceutically-acceptable salts thereof, and combinations thereof. Claims 95-96 and 105-107 depend from claim 82.

Kagan discloses methods for reducing cholesterol in the body by administering particular chemical compounds, which include Applicants' compound VIII (col. 1, line 1 – col. 2, line 12; col. 2, lines 36-40). The disclosure of Kagan is focused on compositions for *oral* administration or *injection* for reducing cholesterol levels, and does not teach or suggest topical administration of the disclosed cholesterol lowering compositions for any purpose, and certainly not formulation of such compositions for percutaneous absorption to reduce skin pigmentation (*see, e.g.,* col. 4, lines 69-75; col. 5, lines 61-66; Examples 1-8; claims 1-2).

Hsia discloses a method of modifying serum cholesterol levels and treating atherosclerosis by topically administering a phospholipid such as phosphatidylcholine to the skin (*see, e.g.*, Abstract; col. 2, lines 64-67). The Office Action states that the composition of Hsia can be a lotion, cream, gel or ointment, and includes a carrier and optionally additional ingredients such as an absorption enhancer (col. 3, lines 1-2 and 21-25; claim 4). Hsia does not teach or suggest a composition including a compound as recited in Applicants' claims for reducing skin pigmentation.

Cohen discloses saccharide compositions, such as low molecular weight heparin, for regulating cytokine activity such as secretion of TNF-α (*see, e.g.*, Abstract; col. 1, lines 20-44). The Office Action relies on Cohen as teaching that the disclosed compositions may have a beneficial effect in atherosclerosis, and states that the compositions can be administered topically and include a cosmetic agent such as a sunscreen (col. 15, lines 43-47; col. 16, lines 11-14; col. 24, lines 26-37 and 42-45). Cohen does not teach or suggest a composition including a compound as recited in Applicants' claims for reducing skin pigmentation.

Okabe discloses a gel pharmaceutical formulation for local anesthesia that provides percutaneous absorption of a local anesthetic, such as a xylidene or aminobenzoic acid compound, when applied to the skin (*see, e.g.*, Abstract; col. 3, lines 33-37). The Office Action cites Okabe for disclosure of polypropylene glycol as a percutaneous absorption enhancer (col. 3, lines 62-67). Okabe does not teach or suggest a composition including a compound as recited in Applicants' claims for reducing skin pigmentation.

Claim 82 is not obvious over Kagan, Hsia, Cohen and Okabe, alone or in combination. None of the cited references provides any teaching or suggestion regarding a topical pharmaceutical composition in the form of an ointment, cream, lotion or emulsion that includes a

dermatologically-acceptable carrier and is formulated for percutaneous absorption to reduce skin pigmentation with a compound as claimed. The Office Action states that it would have been obvious to combine the compound of Kagan with the formulations of Hsia or Cohen, because each of the references discloses treatments for atherosclerosis. Okabe discloses local anesthetic compositions, and is cited merely for disclosing a particular percutaneous absorption enhancer.

Applicants respectfully disagree that there would have been any reason to combine the cited art. Kagan describes the disclosed active ingredients as "3β-(dialkylaminoalkoxy)5-androsten-17-ones, 3β-(dialkylaminoalkoxy)5α-androstan-17-ones, 3β-(dialkylaminoalkoxy)5-androsten-17-one N-oxides, 3β-(dialkylaminoalkoxy)5α-androstan-17-one N-oxides and the physiologically acceptable acid addition salts thereof" (col. 1, lines 13-20).

In stark contrast, Hsia is directed to phospholipids and Cohen is directed to saccharides, completely different types of molecules. Moreover, the passages of Cohen that are cited in the Office Action as supporting topical administration (col. 24, lines 26-37 and 42-45) do not even relate to treatment of atherosclerosis, which is the alleged link supporting the combination with Kagan, and instead relate to adding oligosaccharides to sunscreen preparations to help protect the skin and alleviate skin conditions such as solar erythema.

Thus, disclosures in Hsia and Cohen teaching the application of phospholipids and saccharides in topical formulations would not give one skilled in the art any reason to think that compounds such as those disclosed by Kagan should or even could be applied in similar formulations, particularly when Kagan itself identifies numerous useful alternative formulations.

In *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1731 (2007), the U.S. Supreme Court explained that "[a] patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art." Thus, "it can be important to identify a reason that would have prompted a person of ordinary skill in the art to combine the elements as the new invention does. Inventions usually rely upon building blocks long since uncovered, and claimed discoveries almost necessarily will be combinations of what, in some sense, is already known." *Id.* Accordingly, an analysis supporting the reason to combine prior art teachings "should be made explicit. See *In re Kahn,* 441 F.3d 977, 988 (C.A.Fed.2006) ('[R]ejections on obviousness grounds cannot be sustained by mere conclusory

statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness')." *Id.* at 1741.

Applicants respectfully submit that the Office Action does not provide sufficient particular evidence to demonstrate any reason to combine the teachings of Kagan, relating to oral or parenteral cholesterol lowering compositions of particular steroid compounds, with the teachings of Hsia or Cohen disclosing topical formulations of phospholipids or saccharides, to obtain a topical composition that reduces skin pigmentation, *other than by using Applicants' own disclosure as a blueprint for the combination.* That each of Kagan, Hsia and Cohen discloses compounds potentially useful in treating atherosclerosis, as stated by the Office Action, is not a sufficient reason for one skilled in the art to combine these teachings related to diverse types of agents. This is particularly true given that, as noted above, the cited passages of Cohen regarding topical administration relate to sunscreen compositions rather than treatments for atherosclerosis, and that Kagan effectively teaches away from the use of transdermal or topical delivery systems.

More specifically, Kagan discloses a wide range of *oral* and *parenteral* formulations for administering the disclosed cholesterol lowering compounds (*see, e.g.,* col. 4, line 69 - col. 5, line 66; Examples 1-8). For example, at column 4, lines 70-75, Kagan states that "the novel compositions are suitably presented for administration in unit dosage form as tablets, pills, capsules, powders, wafers, cachets, granules, sterile parenteral solutions or suspensions in aqueous or oil vehicles, oral aqueous or oil dispersions, including syrups and elixirs, and the like." However, Kagan does *not* disclose specific compositions *formulated for percutaneous absorption* by *topical* administration, although the general concept of topical pharmaceutical compositions has been well known for many years. Indeed, by disclosing numerous oral and parenteral dosage forms but failing to disclose topical formulations, the teachings of Kagan suggest to one of ordinary skill in the art that the disclosed compositions would not be effective for their intended purpose when administered topically. Accordingly, the only possible reason to combine the compounds disclosed by Kagan with topical formulations as disclosed by Hsia or Cohen would be based on improperly using Applicants' own disclosure as a roadmap for the combination. There would be even less reason to combine the compounds of Kagan with the

topical formulations of Okabe, which provide for administration of local anesthetics, and thus involve a different indication as well as different types of compounds.

Furthermore, as acknowledged in the Office Action, one of the fundamental factors in any obviousness analysis includes the consideration of objective evidence of nonobviousness. This includes consideration of unexpected results. *See, e.g.*, U.S. Patent and Trademark Office, Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*, 72 Fed. Reg. 57526, 57527 and 57534 (October 10, 2007). The Supreme Court in *KSR* explained that "a combination of familiar elements according to known methods is likely to be obvious *when it does no more than yield predictable results*." *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1731 (2007) (emphasis added). Accordingly, an alleged combination of known elements that produces *unpredictable results*, as the presently claimed invention does, should not be found obvious.

In the present case, any alleged arguments of obviousness based on the cited art are rebutted by the unexpected effects of the claimed compositions in reducing skin pigmentation, as described in the specification (*see, e.g.*, page 7, lines 8-15; page 8, line 32 – page 11, line 3; page 16, lines 21-31; page 18, lines 13-16; page 19, lines 1-6; page 50, lines 23-29; page 56, lines 6-12; Example 6; and Figures 15-16). *See, e.g., In re Soni*, 54 F.3d 746 (Fed. Cir. 1995). The inventors determined that agents capable of modifying late endosomal/lysosomal trafficking, such as the compounds recited in claim 82, are useful for reducing skin pigmentation, because they alter the trafficking of proteins necessary for melanin synthesis, and decrease melanin production. Prior to this discovery, one of ordinary skill in the art would not have expected the compounds recited in claim 82 to have an effect on melanin production or skin pigmentation. Thus, there would have been no reason to formulate the compounds in topical compositions for percutaneous absorption. The experimental results described in Example 6 and illustrated in Figures 15-16 demonstrate the previously unknown and unexpected effect on skin pigmentation of the compounds recited in claim 82. These results demonstrate for the first time that compounds II-VIII decrease melanin production in melanocytes (*see* Specification, page 79, lines 18-27; page 50, lines 23-29; and Figures 15-16). Thus, as described and demonstrated by experimental evidence presented in the specification, the claimed topical compositions provide

the previously unknown and beneficial effect of decreasing melanin production, and thus reducing skin pigmentation.

The language of Applicants' claim 82 specifically reflects these unexpected results, emphasizing that the claimed "pharmaceutical composition *for reducing skin pigmentation*" includes a "*skin pigmentation reducing effective amount* of a compound." Furthermore, the claimed pharmaceutical composition includes a "*dermatologically* acceptable carrier," and takes the form of "*an ointment, cream, lotion or emulsion* formulated for *percutaneous absorption* by *topical administration*." Thus, the claim explicitly refers to and incorporates the unexpected results demonstrating the non-obviousness of the claimed compositions, namely, the unexpected effects of the compounds in reducing skin pigmentation when applied in a composition formulated for topical administration.

In this regard, Applicants note that nonobviousness of a claimed chemical composition can be established based on the composition's unexpected activity in performing a certain function. *See, e.g., In re Chupp*, 816 F.2d 643 (Fed. Cir. 1987) (unexpected results demonstrating herbicidal activity in two crops established nonobviousness of claimed chemical compound and corresponding herbicidal composition); *see also, In re Soni*, 54 F.3d 746 (Fed. Cir. 1995) (PTO erred in giving insufficient weight to unexpected results in specification regarding performance properties of claimed polymer composition). In this case, the unexpected effects of the claimed topical compositions in reducing skin pigmentation, as described in the specification, are sufficient to overcome any alleged grounds of obviousness.

In sum, obviousness has not been established, and any alleged basis for obviousness based on the cited art is rebutted by the unexpected effects of the claimed compositions in reducing skin pigmentation.

Accordingly, Applicants respectfully submit that claim 82 and its dependent claims are not obvious in view of the cited references alone or in combination, and request that the present rejections under § 103(a) be reconsidered and withdrawn.

III. Conclusion

In view of the arguments set forth above, Applicants respectfully submit that the objections and rejections contained in the Office Action mailed on November 2, 2007 have been overcome, and that the pending claims are in condition for allowance.

Applicants hereby petition for a one-month extension of time to respond to the Office Action of November 2, 2007. Please charge the $120.00 fee for this purpose, as well as the $180.00 fee for the Information Disclosure Statement submitted herewith, to our Deposit Account No. 08-0219. No other fees are believed to be due in connection with this correspondence. However, please charge any payments due or credit any overpayments to our Deposit Account No. 08-0219.

It has come to the Applicants' attention that initialed copies of the Forms SB-08 submitted on July 12, 2006, February 21, 2007, April 19, 2007, July 17, 2007 and January 24, 2008, have not yet been received. Applicants respectfully request that, in addition to the Form SB-08 of the Information Disclosure Statement submitted herewith, that the examiner return initialed copies of the above Forms SB-08 with the next Office Action.

The Examiner is encouraged to telephone the undersigned at the number listed below in order to expedite the prosecution of this application.

Respectfully submitted,

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Date: 2/19/08

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